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Original Article

A nomogram for calculating the maximum dose of local anaesthetic*

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Summary

Toxic dose limits ($mg.kg^{-1}$) for local anaesthetics based on body weight are well-established, but calculation of the maximum safe volume (ml) of a given agent and formulation is complex, and frequently results in errors. We therefore developed a nomogram to perform this calculation. We compared the performance of the nomogram with a spreadsheet and a general purpose calculator using simulated clinical data. Bland-Altman analysis showed close agreement between the nomogram and spreadsheet, with bias of −0.07 ml and limits of agreement of −0.38 to +0.24 ml (correlation coefficient $r^2 = 0.9980$; $p < 0.001$). The nomogram produced fewer and smaller errors compared with the calculator. Our nomogram calculates the maximum safe volume (ml) of local anaesthetic to a clinically acceptable degree of accuracy. It facilitates rapid cross-checking of dosage calculations performed by electronic or other means at negligible cost, and can potentially reduce the incidence of local anaesthetic toxicity.

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Introduction

Local anaesthetics are increasingly used worldwide for infiltration, peripheral and regional anaesthesia, and neuraxial blockade by a wide range of clinicians including surgeons, anaesthetists, general practitioners, obstetricians, dentists, nurses and paramedics. It is difficult to assess the total annual usage of these agents, but an estimated 300 million cartridges of local anaesthetic are used per year by American dentists alone [1].

Although typically safer than general anaesthesia, overdosage and toxicity are associated with significant mortality and morbidity, occurring in ~1 in 1000 patients [2]; with possibly many other cases unrecognised and unreported. Local anaesthetic systemic toxicity is a multifactorial phenomenon that depends on individual pharmacokinetics and pharmacodynamics [3], but guidelines for maximum doses are widely accepted for all agents in common use [4].

Drug dose calculation is usually performed using one of the following techniques: mental calculation with or without the aid of a pen and paper; a general purpose calculator; or a dedicated computer program or smart phone 'app'. The calculation may also be performed using a graphic aid that is specific to the calculation (e.g. a table, graph, specialist slide rule or nomogram). Nomograms provide a simple, low-cost

method of primary calculation, and a means of cross-checking calculations that have been performed by other methods. We have therefore developed a nomogram to aid calculation and facilitate cross-checking of the maximum recommended doses of local anaesthetic agents.

Methods

Design and development

For any given agent:

$$\text{Dose (mg)} = \text{Concentration (mg.ml}^{-1}\text{)} \times \text{Volume (ml)}$$

Rearranging for volume:

$$\text{Volume (ml)} = \frac{\text{Dose (mg)}}{\text{Concentration (mg.ml}^{-1}\text{)}}$$

It follows that:

$$\text{Maximum volume (ml)} = \frac{\text{Body weight (kg)} \times \text{Maximum dose (mg.kg}^{-1}\text{)}}{\text{Concentration (mg.ml}^{-1}\text{)}} \quad (1)$$

For any given local anaesthetic agent and formulation, Maximum dose ($mg.kg^{-1}$) and Concentration ($mg.ml^{-1}$) are constants. We can therefore define a Dosage factor ($ml.kg^{-1}$) for any given agent and formulation as:

$$\text{Dosage factor (ml.kg}^{-1}\text{)} = \frac{\text{Maximum dose (mg.kg}^{-1}\text{)}}{\text{Concentration (mg.ml}^{-1}\text{)}} \quad (2)$$

Thus, for 0.5% plain bupivacaine: Maximum dose = 2 $mg.kg^{-1}$ and Concentration = 5 $mg.ml^{-1}$; therefore: Dosage factor = 2 $mg.kg^{-1}$ ÷ 5 mg.ml = 0.4 $ml.kg^{-1}$

Substituting for Dosage factor, taking logarithms, and re-arranging:

$$0 = \ln(\text{Body weight (kg)}) + \ln[\text{Dosage factor (ml.kg}^{-1}\text{)}] - \ln(\text{Maximum volume (ml)}) \quad (3)$$

This is the standard algebraic form required to design a third class genus zero (parallel alignment) nomogram [5].

Dosage factor was calculated for 14 commonly used local anaesthetic agents and formulations (Table 1). We considered adding additional scale markers for the L-enantiopure preparations of bupivacaine, as the maximum safe dosage for these formulations is slightly greater than that of the corresponding racemic mixtures. However, we elected to use the toxic dose limit of the racemic mixture for all preparations, as this ensured that the nomogram remained simple to use, while incorporating an increased margin of safety whenever the L-enantiopure form was substituted for the racemic form.

Equation (3) was then converted to matrix determinant form (4) to facilitate drafting, and matrix transformations were applied to optimise the layout for A4 landscape page format [5, 6]:

$$0 = \begin{vmatrix} 0 & \ln(\text{Dosage factor}) & 1 \\ 1 & \ln(\text{Body weight}) & 1 \\ 0.5 & \frac{\ln(\text{Volume})}{2} & 1 \end{vmatrix} \quad (4)$$

Computer software was used to aid calculation (Excel®; Microsoft Corp., Redmond, WA, USA) and drafting (PyNomo, www.pynomo.org; Rhinoceros®; McNeel North America, Seattle, WA, USA; Illustrator®; Adobe Systems Inc, San Jose, CA, USA) of the nomogram; and the results were cross-checked by manual calculation.

Principles of graphic design and human factors research were applied to optimise legibility, usability and precision, and minimise potential for error [7]. Features include: simplification of procedures for use; removal of all extraneous information; grouping of similar drugs on each side of the 'Agent' axis; and a 'key' (thumbnail diagram) showing method of use (Fig. 1). Legibility is maximised through optimal size, spacing and hierarchy of scale graduations and numbering [5]; and use of a specialist typeface [8]. Drug names and concentrations are emphasised and differentiated through the use of 'Tall Man' lettering and highlighting [9]. Scale graduations have been chosen to correspond to those found on a standard syringe of appropriate volume, and logarithmic scales are used to provide increased precision at the clinically significant lower end of the scale ranges.

The reverse of the nomogram carries information about toxic dose limits, signs and symptoms of overdosage, and a protocol for management of local anaesthetic toxicity (Fig. 2) [10]. The latter includes a

Table 1 Commonly used preparations of local anaesthetics. Preparations with the lowest dosage factor have greatest potential for toxicity, and vice-versa.

Agent	Concentration; % w/v	Concentration; $mg.ml^{-1}$	Maximum dose; $mg.kg^{-1}$	Dosage factor; $ml.kg^{-1}$ *
Lidocaine	1	10	3	0.3
	2	20	3	0.15
Lidocaine with adrenaline	1	10	6	0.6
	2	20	6	0.3
Prilocaine	1	10	6	0.6
	2	20	6	0.3
Prilocaine with adrenaline	1	10	8	0.8
	2	20	8	0.4
Bupivacaine	0.25	2.5	2	0.8
	0.5	5	2	0.4
Bupivacaine with adrenaline	0.25	2.5	2.5	1.0
	0.5	5	2.5	0.5
Ropivacaine	0.75	7.5	3	0.4
Ropivacaine with adrenaline	0.75	7.5	4	0.53

*Dosage factor $(ml.kg^{-1}) = \frac{\text{Maximum dose } (mg.kg^{-1})}{\text{Concentration } (mg.ml^{-1})}$

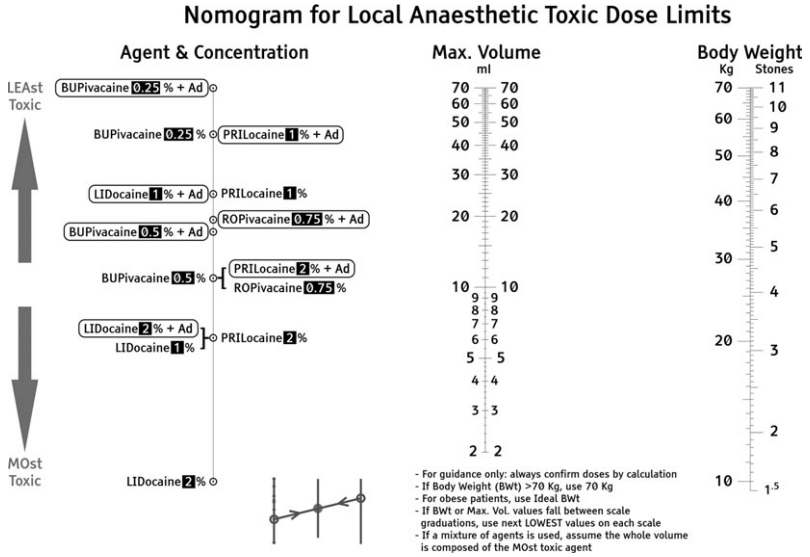

Figure 1 Nomogram for local anaesthetic toxic dose limits (front). This Figure may be downloaded/copied for non-commercial purposes without seeking permission so long as the source is quoted: Williams DJ, Walker JD. A nomogram for calculating maximum dose of local anaesthetic. *Anaesthesia* 2014; doi: 10.1111/anae.12679.

four-axis conversion scale (designed using standard mathematical techniques [5]) to help the user to confirm rapidly the correct initial bolus (ml), infusion rate ($ml.h^{-1}$) and maximum dose (ml) of intravenous lipid emulsion. To use this, the user simply draws a vertical line on the scale at the value corresponding to the patient's body weight, and reads the other parameters at the point of intersection of the line with the other three axes. An example for a patient weighing 70 kg is shown by the dashed line.

The nomogram was printed double-sided on to A4 paper and laminated; however, it could be printed onto waterproof paper or plastic slates for greater durability. If designed for single-patient use and subsequent inclusion in the patient's records, the design could be printed at low cost on to paper charts, with

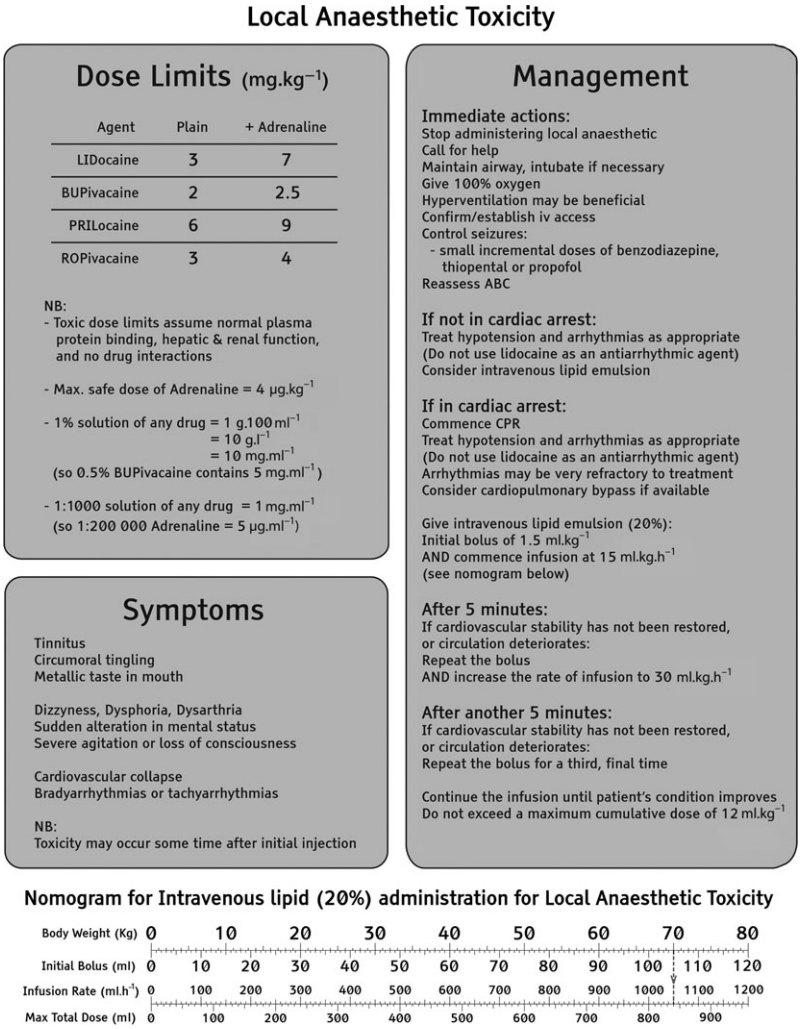

Figure 2 Nomogram for local anaesthetic toxic dose limits (reverse), including nomogram to aid calculation of intravenous lipid administration. An example for a patient weighing 70 kg is shown by the vertical dashed line. (Adapted from: Association of Anaesthetists of Great Britain and Ireland. *Management of Severe Local Anaesthetic Toxicity*. London: AAGBI, 2010; and Di Gregorio G, Neal JM, Rosenquist RW, Weinberg GL. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Regional Anesthesia and Pain Medicine* 2010; **35**: 181-7). This figure may be downloaded/copied for non-commercial purposes without seeking permission so long as the source is quoted: Williams DJ, Walker JD. A nomogram for calculating maximum dose of local anaesthetic. *Anaesthesia* 2014; doi: 10.1111/anae.12679.

space added to include the patient's details and date of administration of the local anaesthetic.

Instructions for use

Each agent and concentration has its own reference point on the left-hand scale. A line drawn from this point to the patient weight scale will indicate the corresponding recommended maximum volume where it intersects the middle scale. Users are instructed to use ideal body weight, and to use a body weight of 70 kg for patients weighing 70 kg or more. Where values for body weight and/or maximum volume fall between scale graduations, the next lowest scale graduation for each parameter should be used in order to maximise the margin of safety and prevent potential error due to incorrect interpolation between the logarithmic scale markings. If a mixture of two different formulations of local anaesthetics is administered, users should perform the calculation as if the whole volume used were composed of the agent with the greater toxic potential

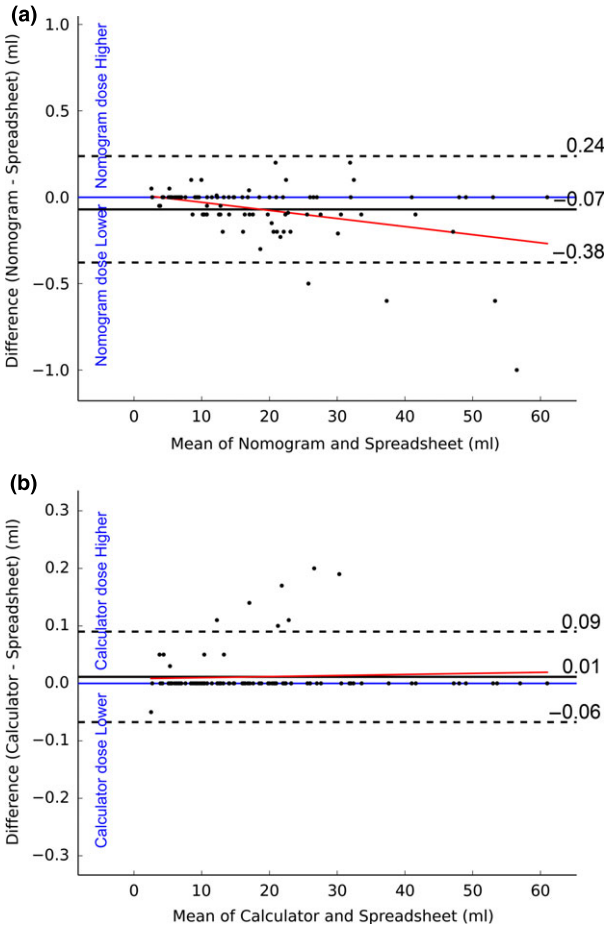

Figure 3 (a) Bland–Altman plot of mean maximum permitted volume vs difference in maximum permitted volume (Nomogram vs Spreadsheet) for 100 randomly-generated sets of simulated patient data, showing: mean difference (bias) (—) = −0.07 ml; limits of agreement (95% CI = bias ± 1.96 SD) (----) = −0.38 to 0.24 ml; regression line (—): r^2 = 0.99980; and line of equality (difference = 0) (—). (b) Bland–Altman plot of mean maximum permitted volume vs difference in maximum permitted volume (Calculator vs Spreadsheet) for 100 randomly-generated sets of simulated patient data, showing: mean difference (bias) (—) = 0.01 ml; limits of agreement (95% CI = bias ± 1.96 SD) (----) = −0.06 to 0.09 ml; regression line (—): r^2 = 0.999991; and line of equality (difference = 0) (—).

i.e. the agent closest to the bottom of the 'Agent & Concentration' axis, as indicated.

Assessment

Although the mathematical basis of the nomogram is sound, the authors elected to assess its accuracy using methods described previously [6]. A spreadsheet (Excel) was used to generate random 100 sets of simulated patient values for body weight (range 10–70 kg), and type (agent and formulation) of local anaesthetic. The recommended maximum volume of local anaesthetic was calculated by the authors in each case using the nomogram and a general purpose calculator (Casio fx-83 ms; Casio Computer Co. Ltd., Tokyo, Japan).

Bland-Altman analysis was used to compare the values calculated using the nomogram and calculator with correct values calculated by the spreadsheet. No conscious bias was exercised in performing calculations by either method, and the authors were blinded to the correct answers until analysis was completed. For the purposes of validation, volumes falling between scale marks of the nomogram were interpolated; however, in practice the user is advised to read the next lowest value on the scale in order to increase the margin of safety. We considered an error to be present when the dose given by the nomogram or calculator differed from the spreadsheet by 5% or more. For the purposes of analysis, such calculations/readings were re-taken, in accordance with international guidelines [11].

Results

The nomogram correlated well with the spreadsheet. Although the calculator was more accurate when used correctly, the calculator produced more and larger errors than the nomogram (Fig. 3a, b).

Over the course of the validation, five mistakes were made: once using the nomogram and four times using the calculator, corresponding to an error rate of 1% and 4%, respectively. One error occurred using the nomogram, with an underestimate of 3.2 ml in the maximum permissible volume of local anaesthetic. Four errors occurred using the calculator, with a mean overestimate of 130.5 ml in the maximum permissible volume of local anaesthetic (range −10.1 to 514 ml).

The nomogram overestimated the maximum permissible volume for 11 patients, but never by more than 0.2 ml. When used correctly, the nomogram did not underestimate the maximum permissible volume by more than 1 ml, and this only occurred for large volumes (> 50 ml), where this was of little clinical significance.

Discussion

This study demonstrates that it is possible to use a nomogram to calculate maximum recommended doses of local anaesthetic to a high degree of accuracy.

Our nomogram only deals with body weights up to 70 kg, which might be seen as limiting in an increasingly obese population. However, in the case of all the local anaesthetic agents described above, the British National Formulary (BNF) is clear that doses should be calculated based on ideal body weight, which for most adults is 60–75 kg, depending on height and sex. The BNF also specifies maximum doses for certain agents: lidocaine 200 mg; bupivacaine 150 mg; and prilocaine 400 mg; corresponding to body weights of 67 kg, 75 kg, and 67 kg, respectively [12]. We therefore feel that it is incorrect to calculate maximum doses of local anaesthetic based on measured body weight. Body weights > 75 kg are therefore unnecessary on the nomogram, and their absence reminds users that ideal weight should be used. If guidelines are revised in future to include greater body weights, the nomogram could be re-drafted appropriately using the methodology described above.

Our assessment of the nomogram used a relatively small number of calculations and was potentially susceptible to bias. However, the observed trends are consistent with comparable studies, which have shown that both the incidence and the magnitude of errors are lower when a nomogram is used compared with a generic electronic calculator [13, 14]. Furthermore, when errors occurred, the maximum permissible dose tended to be overestimated by the calculator and underestimated by the nomogram. The latter was therefore less likely to result in clinical harm. The incidence of unrecognised keystroke errors when using the calculator was 4%, which is similar to that found in previous studies [13–15]; errors involved a doubling or halving of the dose, except in one case of a tenfold dosage error.

Mental calculation and general purpose calculators have no built-in system for detecting or preventing user input errors, and require users to remember and apply correctly the appropriate formulae, toxic dose limits and unit conversions. Dedicated software solutions provide rapid calculation, integrated formulae and error checking, but typically require electrical power and an internet connection, rarely produce a hard copy of the calculation, and may contain latent coding errors that render them vulnerable to rare but extreme errors [16]. Nomograms are very low cost and robust, and produce results more rapidly than manual or electronic calculation with fewer and smaller errors [13, 14]. They are resistant to data entry errors, because all input and output scales are confined to appropriate clinical ranges. Errors due to incorrect recollection or application of formulae cannot occur because nomograms are graphical embodiments of algebraic formulae. Lines drawn onto a printed copy of a nomogram simultaneously perform the calculation and provide a permanent record of how the calculation was performed. The precision of a nomogram is typically limited to three significant digits due to practical restrictions of scale size and the visual acuity of the user; however, this is sufficient for most medical applications.

In a hospital setting, medication errors occur in up to 6.5% of patients and account for 20% of all adverse patient events, yet are one of the most readily preventable forms of error. More than one in six medication errors are due to drug dose miscalculation or incorrect conversion of units [17]. The drugs most commonly involved include the local anaesthetic lidocaine and the vasoactive agent adrenaline, which is frequently added to local anaesthetic solutions to prolong the duration of action. For historical reasons, the concentration of local anaesthetic agents is still frequently expressed as percentage weight-in-volume (% w/v) and the concentration of adrenaline is still expressed as a ratio (1:n000). These units are poorly understood by medical students and clinicians of all levels of experience [18, 19]. Not only must clinicians correctly recall and apply the maximum recommended doses for a given agent or combination of agents; but they must also convert non-standard units of concentration into $mg.ml^{-1}$. These additional steps in computation, combined with task loading or time pressure, can result in potentially fatal dosage errors [17–19].

Cross-checking of calculations is mandatory in other safety-critical fields such as aviation and diving.

Two users should independently perform calculations using two completely different methods: a dedicated electronic device (e.g. flight computer); and a dedicated graphic device (e.g. aviation nomogram). The currently recommended 'buddy' system in medicine, where two users perform calculations independently using the same method, is not a sufficient safeguard to prevent catastrophic drug dosage errors [20].

Validation allows users to be confident that calculation methods provide accurate and reproducible results. Previously, nomograms have simply been presented and accepted. We believe that this is the first time that a nomogram for drug dose calculation has been formally assessed, and hope that this provides a model for validation of other calculation methods, including electronic 'apps'. Future work will evaluate the nomogram and compare its performance with other methods of calculation in clinical practice. We are currently developing a version of the nomogram for use in dentistry.

Drug dosage calculation errors are a significant cause of mortality and morbidity. Dosage calculation errors involving local anaesthetics are particularly prevalent due to the widespread use of these agents, and the fact that the concentrations of these agents are frequently presented in non-standard units. Different methods of drug dosage calculation have different strengths and weaknesses; and no single method can guarantee error-free calculation. However, our nomogram allows drug dose calculations performed by electronic or other means to be rapidly cross-checked at negligible cost, and can potentially reduce the incidence of local anaesthetic toxicity and improve patient safety.

Competing interests

No competing interests and no external funding declared.

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